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(54) 4-Benzyl-5-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-ones and their use as anticonvulsants.

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EP-A- 0 273 310
US-A- 3 621 099
US-A- 4 966 909

INDIAN JOURNAL OF CHEMISTRY vol. 9, no. 6, June 1990, NEW DELHI IN pages 642 - 646; S. HUSAIN ET AL: '3,4-Disubstituted 5-Hydroxy-1,2,4-triazoles Derived from 4-Substituted Semicarbazones'

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EP 0 435 177 B1

Description

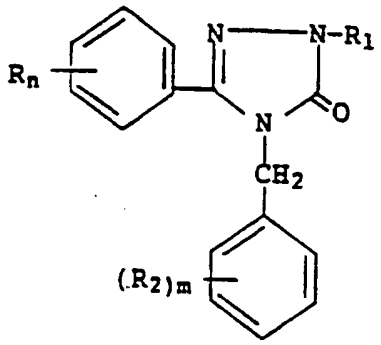
This invention relates to 4-benzyl-5-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-ones and their use as anticonvulsant agents for the treatment of seizure disorders.

In EP-A-0 273 310, 5-aryl-3H-1,2,4-triazol-3-ones are disclosed having anticonvulsant properties. The nitrogen in the 4-position of the triazole ring is substituted with a C_{1-6} alkyl group.

US-A-3,621,099 describes 1H,1,2,4-triazole-3,5-(2H,4H)-dione derivatives which may be used as anticonvulsants.

The Indian J. Chem. (1971) vol. 9, pp. 642-646 describes the synthesis of 3,4 disubstituted 5-hydroxy 1,2,4-triazoles, including 5-phenyl-4-benzyl-2,4-dihydro-3H-1,2,4-triazole-3-one and 5-(4-methoxyphenyl)-2,4 dihydro-4-benzyl-3H-1,2,4 triazole-3-one.

More specifically this invention relates to compounds of the formula



I

and the tautomers thereof, wherein

R_1 is hydrogen or C_{1-4} alkyl;

R and R_2 are independently C_{1-4} alkyl, C_{1-4} alkoxy, halogeno or trifluoromethyl, and m and n are independently zero, 1 or 2;

or $(R_2)_m$ is methylenedioxy.

R and R_2 preferably represent halogeno, specially chloro or fluoro, with chloro being more preferred. Compounds wherein R is trifluoromethyl also are preferred. R_1 is preferably methyl, although any straight or branched C_{1-4} alkyl group may be used. Compounds wherein R_1 is hydrogen are also preferred. The tautomeric forms are included for each of the compounds embraced within formula I wherein R_1 is H.

Preferably n is one, representing a mono-substituted phenyl moiety with the R-substitutent being located at the ortho, meta or para position, although the ortho- and para-substituted compounds are preferred. When the phenyl moieties are disubstituted (i.e., m or n is 2), substitution may be at the 2,3-; 2,4- ; 2,5-; 2,6-; 3,4-; and 3,5-positions. When $(R_2)_m$ is methylenedioxy, substitution may be in either the 2,3- or 3,4-positions of the benzyl group.

The pharmacological profile of these compounds and their relative potencies may readily be demonstrated through standard laboratory tests indicative of compounds known to be useful as anticonvulsants suitable for use in the treatment of seizure disorders. Compounds of formula I are particularly useful for treatment of epilepsy, but their activity in a broad spectrum of laboratory tests is indicative of activity against most types of seizure disorders.

For example, to evaluate and characterize the anticonvulsant and GABAergic activity and to observe the pharmacological profile of the compounds of this invention, it is convenient to employ such tests as the antagonism of 3-mercaptopropionic acid-induced convulsions, an assay performed on mice wherein wild running fits or generalized seizures are induced by 3-mercaptopropionic acid; the antagonism of strychnine-induced seizures in mice, an assay performed in mice wherein seizures are induced by strychnine; the antagonism to maximal electroshock, an assay performed in mice wherein seizures are caused by the administration of electroshock; and the antagonism to pentylenetetrazol, an assay to measure the prevention of seizures caused by administration of pentylenetetrazol.

Compounds that inhibit pentylenetetrazol-induced seizures in mice are known to possess anticonvulsant and antianxiety effects. An appropriate dose of test compound is administered to groups of mice and, at a selected time thereafter, pentylenetetrazol, prepared as a solution in distilled water such that 10 ml/kg delivers a dose of 60 mg/kg, is administered by rapid intravenous injection. Absence of clonic convulsions

for 2 minutes after pentylenetetrazol is considered significant protection. Prevention of tonic extensor convulsions is also reported and usually occurs at a dose lower than that required to block clonic convulsions. Inhibition of clonic seizures induced by this dose of pentylenetetrazol is evidence of potential anticonvulsant/antianxiety activity. Against seizures caused by pentylenetetrazol, 5-(4-chlorophenyl)-2,4-dihydro-4-benzyl-2-methyl-3H-1,2,4-triazol-3-one has an ED_{50} of 22.6 mg/kg.

In the test for antagonism to maximal electroshock, small groups of mice are administered one or more doses of test compound. At a selected time thereafter, an electroshock sufficient to cause tonic extension in 100% of control mice is administered by means of corneal electrodes. The shock parameters are 50 mA, 120 V, 0.2 seconds. Inhibition of the tonic extensor component of the electroshock convulsion is indicative of anticonvulsant activity of the test material. Phenobarbital blocks in the dose range of 15-30 mg/kg, diphenylhydantoin in the range of 7.5-15 mg/kg. Both of these compounds are effective versus grand mal epilepsy. In this assay, 5-(4-chlorophenyl)-2,4-dihydro-4-benzyl-2-methyl-3H-1,2,4-triazol-3-one has an ED_{50} between 50 and 100 mg/kg.

Patients suitable for treatment with anticonvulsant compositions containing compounds of formula I include warmblooded animals suffering from seizure disorders, for example, mammals such as humans, dogs, cats, horses, pigs, cattle, sheep, rats and mice. The compounds of this invention will exert anticonvulsant activity useful in the treatment of epilepsy and of other seizure disorders at oral dosage levels of about 0.25 to 25 mg/kg of body weight per day. Such doses are much lower than the doses at which these compounds exhibit sedative action and are well below toxic doses of the compounds. Of course the degree of severity of the disease, the age of the patient and other factors normally considered by the attending diagnostician will influence the individual regimen for each patient. In general, the parenterally administered doses are about 1/4 to 1/2 those of orally administered doses.

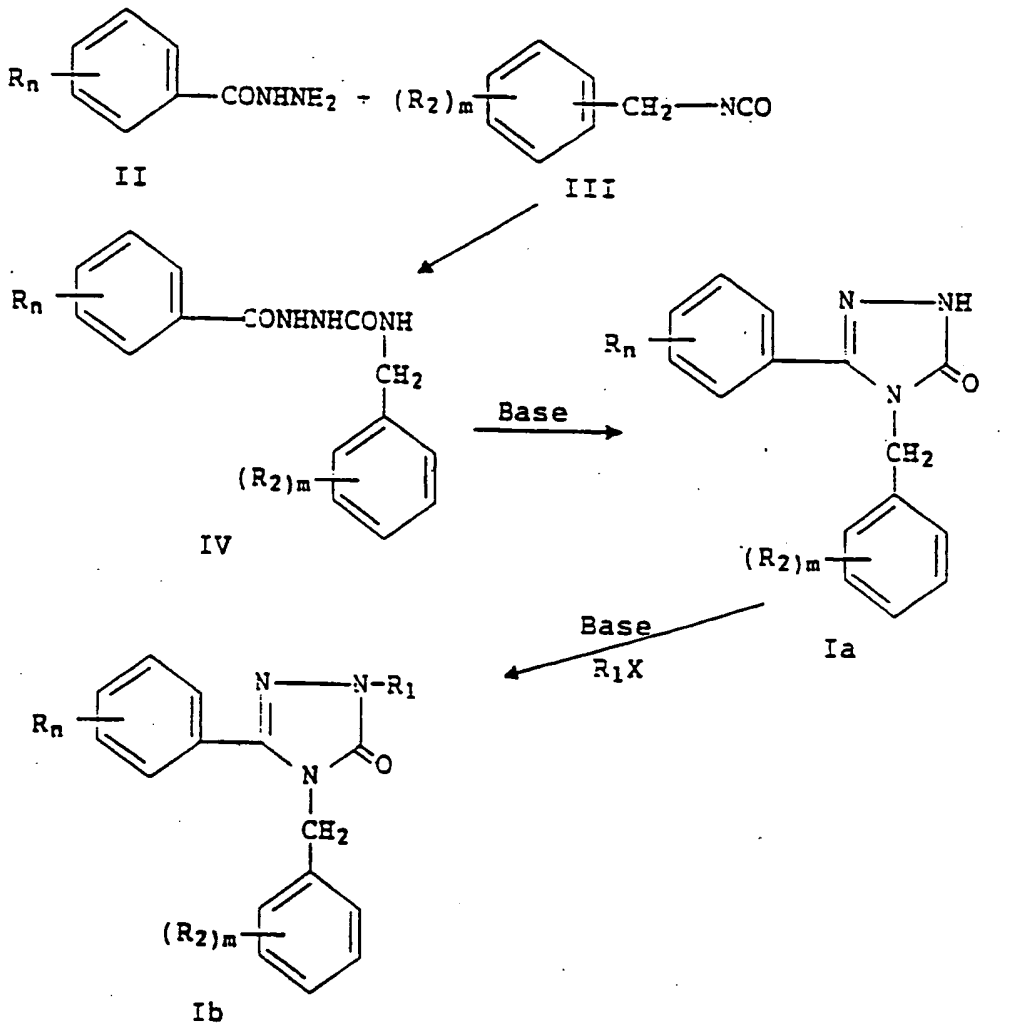
For oral administration the compounds can be formulated into solid or liquid preparations such as capsules, pills, tablets, troches, powders, solutions, suspensions or emulsions. Solid unit dosage forms can be in the form of a capsule which can be of the ordinary gelatin type containing, for example, lubricants and inert fillers such as lactose, sucrose or cornstarch. In another embodiment the compounds of general formula I can be tableted with conventional tablet bases such as lactose, sucrose and corn-starch, in combination with binders such as acacia, corn-starch or gelatin, disintegrating agents such as potato starch or alginic acid, and a lubricant such as stearic acid or magnesium stearate.

For parenteral administration, the compounds may be administered as injectable dosages of a solution or suspension of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid such as water, alcohol, oils and other acceptable organic solvents, with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. Illustrative of oils which can be employed in these preparations are those of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil and mineral oil. In general, water, saline, aqueous dextrose and related sugar solutions, ethanol, glycols such as propylene glycol or polyethylene glycol, or 2-pyrrolidone are preferred liquid carriers, particularly for injectable solutions.

The compounds can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic®, a silicone rubber manufactured by the Dow-Corning Corporation.

As is true for most classes of compounds generally suitable as therapeutic agents, certain subgeneric groups and specific members of that class, in the light of their overall biological profile, are preferred. In this instance the preferred R substituent is chloro, with chloro at the 2- or 4-positions of the aromatic ring being preferred. It is preferred that the R_2 substituent be chloro, fluoro or trifluoromethyl when m is one or two, with hydrogen and methyl being the preferred groups for R_1. A particularly preferred compound is 5-(4-chlorophenyl)-2,4-dihydro-4-benzyl-2-methyl-3H-1,2,4-triazol-3-one.

The compounds of Formula I may readily be prepared using processes and techniques analogously known in the art, for example in the method of S. Kuboda and M. Uda, Chem. Pharm. Bull. 21, 1342 (1979), as seen by the following reaction scheme:



wherein R, n, m, R_1 and R_2 are as defined in formula I, and X is a suitable leaving group.

The preparation of the 1-benzoyl-4-benzylsemicarbazides (IV) is readily effected by reacting a hydrazide (II) with a benzylisocyanate (III) by contacting the reactants together in a suitable aprotic solvent, preferably one in which the hydrazide reactant is soluble, e.g., tetrahydrofuran (THF), $CHCl_3$, CH_2Cl_2, benzene, toluene, Et_2O and the like. The reaction is quite rapid and may be carried out at from 0 °C to about room temperature and, although the reaction proceeds rapidly, the mixture may be left for 24 hours without any significant decrease in yield. The required hydrazides and isocyanates are readily available, but may be prepared by known techniques quite obvious to one of ordinary skill in the art.

The desired 4-benzyl-5-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-ones(Ia) may be prepared by reacting the semicarbazides (IV) with a base, preferably an aqueous alkali metal hydroxide (e.g., NaOH, KOH) at about 50-120 °C, although reflux temperatures are preferred. Normal reaction time is about 7 hours, although 4-24 hours may be needed depending on the temperature of the mixture and the structure of the reactant.

The desired 2,4-disubstituted-2,4-dihydro-3H-1,2,4-triazol-3-ones (Ib) may be prepared by reacting the 4-benzyl-5-phenyl-2,4-dihydro-3H-1,2,4-triazol-3-ones (Ia) with an appropriate R_1X reactant wherein X is a suitable leaving group, e.g., Cl, Br, OSO_2CF_3 and the like. Preferably the reaction takes place in a solution of an aqueous alkali metal hydroxide, (e.g., KOH, NaOH) although more reactive bases (e.g., NaH, KH, LDA) may be used if the reaction is affected under aprotic dry conditions. The reaction preferably takes place at room temperatures over periods of about 18 hours to two weeks.

The following specific examples are given to illustrate the preparation of the compounds of this invention.

Preparation of Intermediate 1-Benzoyl-4-benzylsemicarbazides

EXAMPLE 1

1-(4-Chlorobenzoyl)-4-benzylsemicarbazide

A stirred suspension of 4-chlorobenzoic acidhydrazide (10.4932 g, 6.1508 x 10^{-2} mole) and dry THF (240 mL) was warmed with a heat gun until it was homogenous. To this stirred solution was added benzyl isocyanate (7.8 ml, 6.3 x 10^{-2} mole). After stirring overnight at room temperature, the reaction mixture was diluted with ether. The precipitate was collected by filtration, washed with a little ether, and dried by suction. Crystallization from ethanol afforded small colorless needles: 15.69 g (84%), mp 244-246 • C.

Preparation of 5-Phenyl-4-benzyl-2,4-dihydro-3H-1,2,4-triazol-3-ones

EXAMPLE 2

4-Benzyl-5-(4-chlorophenyl)2,4-dihydro-3H-1,2,4-triazol-3-one

A stirred mixture of 1-(4-chlorobenzoyl)-4-benzylsemicarbazide (16.15 g, 5.317 x 10^{-2} mole) and 1 molar aqueous NaOH (64 ml, 6.4 x 10^{-2} mole) was heated to reflux. After refluxing ca. 22 hrs., the reaction mixture was allowed to cool slightly before being neutralized by the addition of concentrated aqueous HCl (5.5 ml, 6.6 x 10^{-2} mole). A colorless solid formed and after the mixture had cooled to room temperature this was collected by filtration. Crystallization from isopropanol afforded colorless needles: 12.76 g (84%), mp. 208-210 • C.

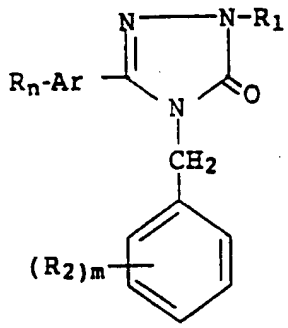
Preparation of 5-Phenyl-2-substituted-4-benzyl-2,4-dihydro-3H-1,2,4-triazol-3-ones

EXAMPLE 3

5-(4-Chlorophenyl)-2-methyl-4-benzyl-2,4-dihydro-3H-1,2,4-triazol-3-one

To a stirred, room temperature, suspension of 4-benzyl-5-(4-chlorophenyl)-3H-1,2,4-triazol-3-one (10.85 g, 3.797 x 10^{-2} mole), 1 molar aqueous NaOH (42 ml, 4.2 x 10^{-2} mole), and ethanol (15 ml) was added methyl iodide (3.6 ml, 5.8 x 10^{-2} mole). After stirring overnight, the reaction was transferred to a separatory funnel where it was extracted with EtOAc (3x). The EtOAc extracts were combined, washed with saturated aqueous NaCl, and dried over anhydrous Na_2SO_4.The drying agent was removed by filtration and the filtrate was evaporated at reduced pressure leaving a yellowish foam. Purification of this foam by a combination of flash chromatography (20% EtOAc/CH_2Cl_2) and crystallization from cyclohexane afforded colorless crystals: 5.92 g (52%), mp 90-91 • C.

In a similar manner the following compounds also may be prepared.

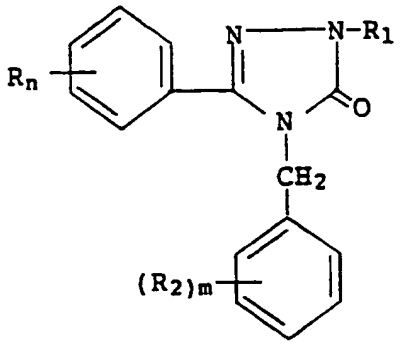


R_n-Ar	R_1	$(R_2)_m$	mp (°C)
Phenyl	H	2,4-Cl_2	145-146
Phenyl	CH_3	2,4-Cl_2	112-114
4-Chlorophenyl	H	2,4-Cl_2	189-191
4-Chlorophenyl	CH_3	2,4-Cl_2	104-106

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula (I)



(I)

wherein R_1 is hydrogen or C_{1-4} alkyl; R and R_2 are independently C_{1-4} alkyl, C_{1-4} alkoxy, halogeno or trifluoromethyl; and m and n are independently zero, 1 or 2; or $(R_2)_m$ is methylenedioxy; excluding, however, compounds I wherein R_1 is hydrogen, m is zero, n is zero or 1 and R is 4-methoxy; and the tautomers and acid addition salts thereof;

2. The compound of Claim 1 wherein R_1 is hydrogen or methyl.

3. The compound of Claim 1 or 2 wherein m is 1 or 2 and R_2 is halogeno.

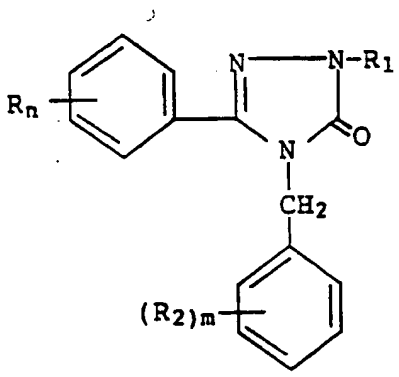
4. The compound of Claim 1 or 2 wherein m is 0.

5. The compound of any of Claims 1 to 4 wherein n is 1 or 2 and R is halogeno.

6. The compound of Claim 5 wherein R is chloro.

7. The compound of Claim 6 wherein the compound is 5-(4-chlorophenyl)-2,4-dihydro-4-benzyl-2-methyl-3H-1,2,4-triazol-3-one.

8. Use of a compound of the formula (I)



(I)

wherein
R_1 is hydrogen or C_{1-4} alkyl;
R and R_2 are independently C_{1-4} alkyl; C_{1-4} alkoxy, halogeno or trifluoromethyl; and
m and n are independently zero, 1 or 2;
or $(R_2)_m$ is methylenedioxy
for the manufacture of a medicament.

9. Use of a compound according to Claim 8 wherein R_1 is hydrogen or methyl.

10. Use of a compound according to Claim 8 or 9 wherein m is 1 or 2 and R_2 is halogeno.

11. Use of a compound according to Claim 8 or 9 wherein m is 0.

12. Use of a compound according to any of Claims 8 to 11 wherein n is 1 or 2 and R is halogeno.

13. Use of a compound according Claim 12 wherein R is chloro.

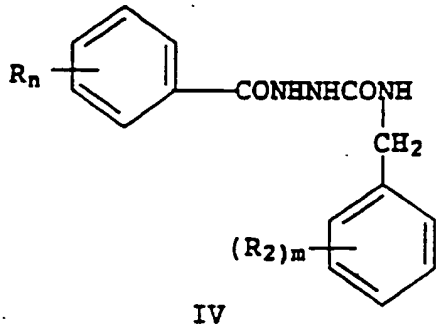
14. Use of a compound according to Claim 13 wherein the compound is 5-(4-chlorophenyl)-2,4-dihydro-4-benzyl-2-methyl-3H-1,2,4-triazol-3-one.

15. Use according to any of Claims 8 to 14 wherein the compound is useful for the treatment seizure disorders.

16. A pharmaceutical composition comprising a compound of the formula (I) as shown in any of Claims 8 to 14 optionally in admixture with a pharmaceutically acceptable carrier and/or diluent.

17. The composition of Claim 16 for the treatment of seizure disorders.

18. A process for the preparation of a compound of the formula (I) according to any of Claims 1 to 7 comprising reacting a semicarbazide of the formula (IV)

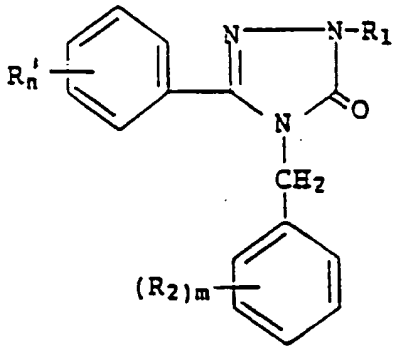


IV

with a base to yield a compound of the formula (I) wherein R_1 is hydrogen, which can then be alkylated to a compound of the formula (I) wherein R_1 is C_{1-4} alkyl, and optionally converting it to an acid addition salt.

Claims for the following Contracting States : GR, ES

1. A compound of the formula (I)



(I)

wherein R_1 is hydrogen or C_{1-4} alkyl; R and R_2 are independently C_{1-4} alkyl, C_{1-4} alkoxy, halogeno or trifluoromethyl; and m and n are independently zero, 1 or 2; or $(R_2)_m$ is methylenedioxy; excluding, however, compounds I wherein R_1 is hydrogen, m is zero, n is zero or 1 and R is 4-methoxy; and the tautomers and acid addition salts thereof;

2. The compound of Claim 1 wherein R_1 is hydrogen or methyl.

3. The compound of Claim 1 or 2 wherein m is 1 or 2 and R_2 is halogeno.

4. The compound of Claim 1 or 2 wherein m is 0.

5. The compound of any of Claims 1 to 4 wherein n is 1 or 2 and R is halogeno.

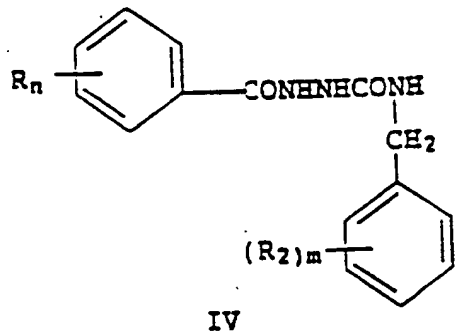
6. The compound of Claim 5 wherein R is chloro.

7. The compound of Claim 6 wherein the compound is 5-(4-chlorophenyl)-2,4-dihydro-4-benzyl-2-methyl-3H-1,2,4-triazol-3-one.

8. A method for the preparation of a pharmaceutical composition comprising combining a compound according to any one of claims 1-7 with a pharmaceutically acceptable carrier.

9. The method according to Claim 8 wherein the pharmaceutical composition prepared is useful for the treatment of seizure disorders.

10. A process for the preparation of a compound of the formula (I) according to any of Claims 1 to 7 comprising reacting a semicarbazide of the formula (IV)



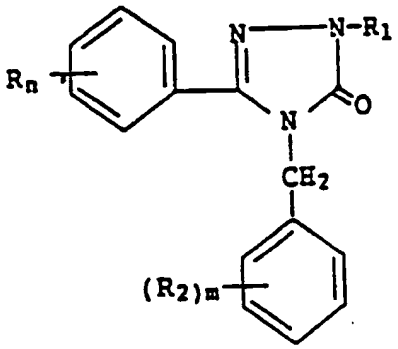
IV

with a base to yield a compound of the formula (I) wherein R_1 is hydrogen, which can then be alkylated to a compound of the formula (I) wherein R_1 is C_{1-4} alkyl, and optionally converting it to an acid addition salt.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel (I)



(I)

in der R_1 ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe ist;
R und R_2 unabhängig eine C_{1-4}-Alkyl-, eine C_{1-4}-Alkoxygruppe, ein Halogenatom oder eine Trifluormethylgruppe sind;
und m und n unabhängig null, 1 oder 2 sind;
oder $(R_2)_m$ eine Methylendioxygruppe ist,
wobei jedoch Verbindungen I ausgeschlossen sind, in denen R_1 ein Wasserstoffatom ist, m null ist, n null oder 1 ist und R eine 4-Methoxygruppe ist;
und tautomere Formen sowie Säureadditionssalze davon.

2. Verbindung nach Anspruch 1, wobei R_1 ein Wasserstoffatom oder eine Methylgruppe ist.

3. Verbindung nach Anspruch 1 oder 2, wobei m 1 oder 2 und R_2 ein Halogenatom ist.

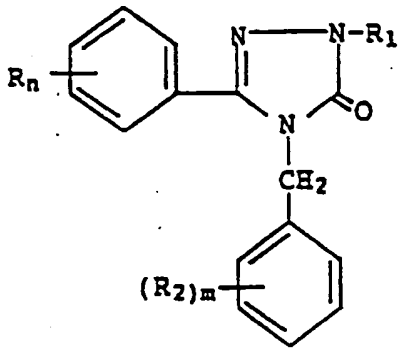
4. Verbindung nach Anspruch 1 oder 2, wobei m 0 ist.

5. Verbindung nach einem der Ansprüche 1 bis 4, wobei n 1 oder 2 und R ein Halogenatom ist.

6. Verbindung nach Anspruch 5, wobei R ein Chloratom ist.

7. Verbindung nach Anspruch 6, wobei diese Verbindung 5-(4-Chlorphenyl)-2,4-dihydro-4-benzyl-2-methyl-3H-1,2,4-triazol-3-on ist.

8. Verwendung einer Verbindung der Formel (I)



(I)

in der R_1 ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe ist;
R und R_2 unabhängig eine C_{1-4}-Alkyl-, eine C_{1-4}-Alkoxygruppe, ein Halogenatom oder eine Trifluormethylgruppe sind;
und m und n unabhängig null, 1 oder 2 sind.
oder $(R_2)_m$ eine Methylendioxygruppe ist,
für die Herstellung eines Medikaments.

9. Verwendung einer Verbindung nach Anspruch 8, wobei R_1 ein Wasserstoffatom oder eine Methylgruppe ist.

10. Verwendung einer Verbindung nach Anspruch 8 oder 9, wobei m 1 oder 2 und R_2 ein Halogenatom ist.

11. Verwendung einer Verbindung nach Anspruch 8 oder 9, wobei m 0 ist.

12. Verwendung einer Verbindung nach einem der Ansprüche 8 bis 11, wobei n 1 oder 2 und R ein Halogenatom ist.

13. Verwendung einer Verbindung nach Anspruch 12, wobei R ein Chloratom ist.

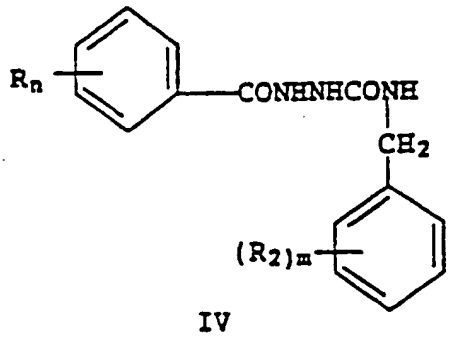
14. Verwendung einer Verbindung nach Anspruch 13, wobei die Verbindung 5-(4-Chlorphenyl)-2,4-dihydro-4-benzyl-2-methyl-3H-1,2,4-triazol-3-on ist.

15. Verwendung nach einem der Ansprüche 8 bis 14, wobei die Verbindung zur Behandlung von Anfallsleiden geeignet ist.

16. Arzneimittel, das eine Verbindung der Formel (I) nach einem der Ansprüche 8 bis 14 gegebenenfalls in Mischung mit einem pharmazeutisch verträglichen Träger und/oder Verdünnungsmittel umfaßt.

17. Zusammensetzung nach Anspruch 16 für die Behandlung von Anfallsleiden.

18. Verfahren zur Herstellung einer Verbindung der Formel (I) nach einem der Ansprüche 1 bis 7, umfassend: Umsetzung eines Semicarbazids der Formel (IV)

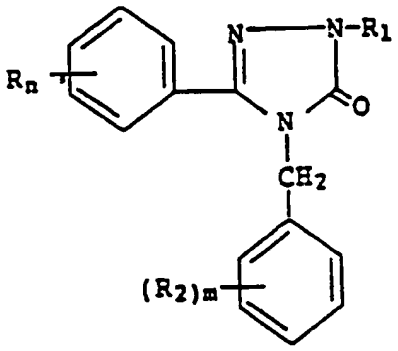


IV

mit einer Base, wodurch eine Verbindung der Formel (I) erhalten wird, in der R_1 ein Wasserstoffatom ist, die anschließend zu einer Verbindung der Formel (I) alkyliert werden kann, in der R_1 eine C_{1-4}-Alkylgruppe ist, und gegebenenfalls Umwandlung dieser Verbindung in ein Säureadditionssalz.

Patentansprüche für folgende Vertragsstaaten : GR, ES

1. Verbindung der Formel (I)



(I)

in der R_1 ein Wasserstoffatom oder eine C_{1-4}-Alkylgruppe ist;
R und R_2 unabhängig eine C_{1-4}-Alkyl-, eine C_{1-4}-Alkoxygruppe, ein Halogenatom oder eine Trifluormethylgruppe sind;
und m und n unabhängig null, 1 oder 2 sind;
oder $(R_2)_m$ eine Methylendioxygruppe ist,
wobei jedoch Verbindungen I ausgeschlossen sind, in denen R_1 ein Wasserstoffatom ist, m null ist, n null oder 1 ist und R eine 4-Methoxygruppe ist;
und tautomere Formen sowie Säureadditionssalze davon.

2. Verbindung nach Anspruch 1, wobei R_1 ein Wasserstoffatom oder eine Methylgruppe ist.

3. Verbindung nach Anspruch 1 oder 2, wobei m 1 oder 2 und R_2 ein Halogenatom ist.

4. Verbindung nach Anspruch 1 oder 2, wobei m 0 ist.

5. Verbindung nach einem der Ansprüche 1 bis 4, worbei n 1 oder 2 und R ein Halogenatom ist.

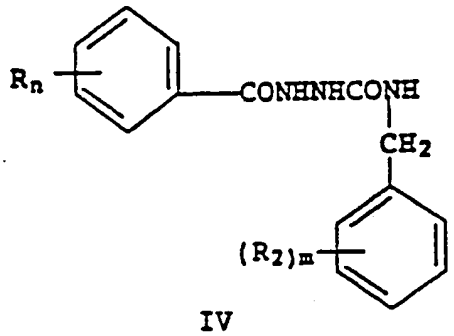
6. Verbindung nach Anspruch 5, wobei R ein Chloratom ist.

7. Verbindung nach Anspruch 6, wobei diese Verbindung 5-(4-Chlorphenyl)-2,4-dihydro-4-benzyl-2-methyl-3H-1,2,4-triazol-3-on ist.

8. Verfahren zur Herstellung eines Arzneimittels, umfassend das Vereinen einer Verbindung gemäß einem der Ansprüche 1 bis 7 mit einem pharmazeutisch verträglichen Träger.

9. Verfahren nach Anspruch 8, wobei das Arzneimittel zur Behandlung von Anfallsleiden geeignet ist.

10. Verfahren zur Herstellung einer Verbindung der Formel (I) nach einem der Ansprüche 1 bis 7, umfassend:
Umsetzung eines Semicarbazids der Formel (IV)

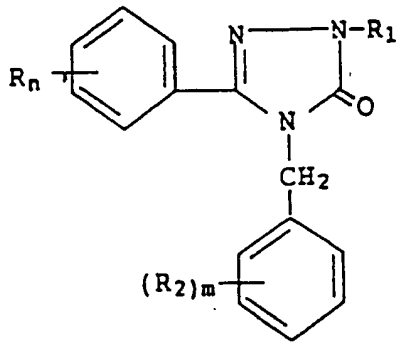


IV

mit einer Base, wodurch eine Verbindung der Formel (I) erhalten wird, in der R_1 ein Wasserstoffatom ist, die anschließend zu einer Verbindung der Formel (I) alkyliert werden kann, in der R_1 eine C_{1-4}-Alkylgruppe ist, und gegebenenfalls Umwandlung dieser Verbindung in ein Säureadditionssalz.

Revendications
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule (I)



(I)

dans laquelle
R_1 est un hydrogène ou un reste alkyle en C_1-C_4; R et R_2 sont indépendamment un reste alkyle en C_1-C_4, alcoxy en C_1-C_4, halogéno ou trifluorométhyle, et m et n sont indépendamment 0, 1 ou 2; ou $(R_2)_m$ est un méthylènedioxy; à l'exclusion cependant des composés I dans lesquels R_1 est un hydrogène, m est 0, n est 0 ou 1 et R est un groupe 4-méthoxy; et leurs tautomères et sels d'addition d'acides.

2. Composé selon la revendication 1, dans lequel R_1 est l'hydrogène ou un groupe méthyle.

3. Composé selon la revendication 1 ou 2, dans lequel m est 1 ou 2 et R_2 est un reste halogéno.

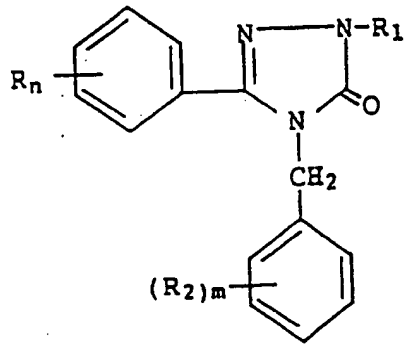
4. Composé selon la revendication 1 ou 2, dans lequel m est 0.

5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel n est 1 ou 2 et R est un reste halogéno.

6. Composé selon la revendication 5, dans lequel R est un reste chloro.

7. Composé selon la revendication 6, où le composé est la 5-(4-chlorophényl)-2,4-dihydro-4-benzyl-2-méthyl-3H-1,2,4-triazole-3-one.

8. Utilisation d'un composé de formule I



(I)

dans laquelle
R_1 est un hydrogène ou un reste alkyle en C_1-C_4;
R et R_2 sont indépendamment un reste alkyle en C_1-C_4, alcoxy en C_1-C_4, halogéno ou trifluorométhyle; et
m et n sont indépendamment 0, 1 ou 2;
ou $(R_2)_m$ est un méthylènedioxy
pour la préparation d'un médicament.

9. Utilisation d'un composé selon la revendication 8, où R_1 est l'hydrogène ou un groupe méthyle.

10. Utilisation d'un composé selon la revendication 8 ou 9, où m est 1 ou 2 et R_2 est un reste halogéno.

11. Utilisation d'un composé selon la revendication 8 ou 9, où m est 0.

12. Utilisation d'un composé selon l'une quelconque des revendications 8 à 11, où n est 1 ou 2 et R est un reste halogéno.

13. Utilisation d'un composé selon la revendication 12, où R est un reste chloro.

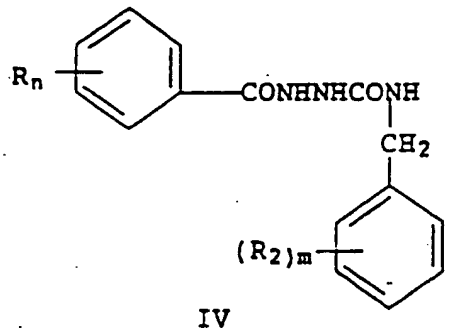
14. Utilisation d'un composé selon la revendication 13, dans laquelle le composé est la 5-(4-chlorophényl)-2,4-dihydro-4-benzyl-2-méthyl-3H-1,2,4-triazole-3-one.

15. Utilisation selon l'une quelconque des revendications 8 à 14, dans laquelle le composé est utile pour le traitement de crises convulsives.

16. Composition pharmaceutique comprenant un composé de formule I selon l'une quelconque des revendications 8 à 14 éventuellement en mélange avec un support et/ou un diluant pharmaceutiquement acceptable.

17. Composition selon la revendication 16 pour le traitement de crises convulsives.

18. Procédé de préparation d'un composé de formule I selon l'une quelconque des revendications 1 à 7, dans lequel on fait réagir un semicarbazide de formule IV

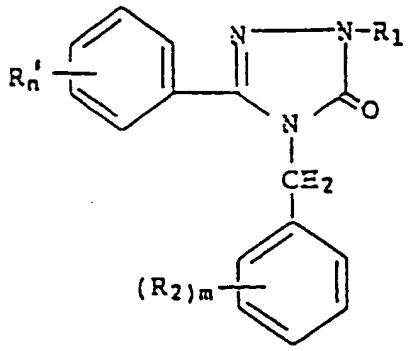


IV

avec une base pour donner un composé de formule (I) dans laquelle R_1 est l'hydrogène, que l'on peut ensuite alkyler en un composé de formule (I) dans laquelle R_1 est un reste alkyle en C_1-C_4, et on le transforme éventuellement en un sel d'addition d'acide.

Revendications pour les Etats contractants suivants : GR, ES

1. Composé de formule (I)



(I)

dans laquelle

R_1 est un hydrogène ou un reste alkyle en C_1-C_4; R et R_2 sont indépendamment un reste alkyle en C_1-C_4, alcoxy en C_1-C_4, halogéno ou trifluorométhyle, et m et n sont indépendamment 0, 1 ou 2; ou $(R_2)_m$ est un méthylènedioxy; à l'exclusion cependant des composés I dans lesquels R_1 est un hydrogène, m est 0, n est 0 ou 1 et R est un groupe 4-méthoxy; et leurs tautomères et sels d'addition d'acides.

2. Composé selon la revendication 1, dans lequel R_1 est l'hydrogène ou un groupe méthyle.

3. Composé selon la revendication 1 ou 2, dans lequel m est 1 ou 2 et R_2 est un reste halogéno.

4. Composé selon la revendication 1 ou 2, dans lequel m est 0.

5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel n est 1 ou 2 et R est un reste halogéno.

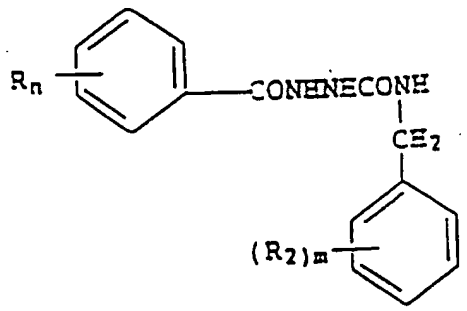
6. Composé selon la revendication 5, dans lequel R est un reste chloro.

7. Composé selon la revendication 6, où le composé est la 5-(4-chlorophényl)-2,4-dihydro-4-benzyl-2-méthyl-3H-1,2,4-triazole-3-one.

8. Méthode de préparation d'une composition pharmaceutique comprenant la combinaison d'un composé selon l'une quelconque des revendications 1 à 7 avec un support pharmaceutiquement acceptable.

9. Méthode selon la revendication 8, dans laquelle la composition pharmaceutique préparée est utile pour le traitement des crises convulsives.

10. Procédé de préparation d'un composé de formule I selon l'une quelconque des revendications 1 à 7, dans lequel on fait réagir un semicarbazide de formule IV



IV

avec une base pour donner un composé de formule (I) dans laquelle R_1 est l'hydrogène, que l'on peut ensuite alkyler en un composé de formule (I) dans laquelle R_1 est un reste alkyle en C_1-C_4, et on le transforme éventuellement en un sel d'addition d'acide.